SPONDYLOARTHRITIS

TYK2 inhibition halts SpA

Targeting the Janus kinase (JAK) TYK2 could have disease-modifying effects in spondyloarthritis (SpA) by halting inflammation and bone erosion, according to new research. In the study, a novel small-molecule inhibitor of TYK2 blocked IL-23 signalling in vitro and inhibited disease progression in mouse models of SpA.

The researchers first showed that the selective TYK2 inhibitor NDI-031407 inhibited IL-23-induced IL-17A production as well as IL-23-induced STAT3 phosphorylation in a dose-dependent manner in human $CD4^+$ T cells. In vivo, in the β-1,3-glucan (curdlan)-triggered SKG mouse model of SpA, treatment with orally delivered NDI-031407 prevented disease progression, as reflected by lower clinical scores for SpA symptoms. Bone erosion, joint space narrowing and bone marrow oedema were also prevented in NDI-031407-treated as compared with vehicle-treated mice. The SpA-associated expansion and activation of T_H17 cells in the draining lymph nodes and arthritic joints of mice was reduced in NDI-031407-treated mice. In a different model of SpA, induced by delivery of minicircle DNA expressing *IL23*, the TYK2 inhibitor also protected against clinical disease driven by systemic IL-23 expression.

Addressing the biologic relevance of *TYK2* single-nucleotide polymorphisms (SNPs) that have been associated with ankylosing spondylitis (AS) in genome-wide association studies, the researchers found that carriage of certain *TYK2* SNPs was associated with a decreased T_H1 cell frequency and a progressive AS phenotype characterized by a high rate of vertebral fusion.

Previous studies have suggested that pan-JAK inhibitors, such as tofacitinib, could be useful for the treatment of SpA. These latest findings suggest that TYK2 has a role in the pathogenesis of AS, and that specific inhibition of TYK2 inhibits disease progression in animal models of SpA. The researchers propose that a small-molecule TYK2 inhibitor could be explored as a potential disease-modifying therapy for AS.

Sarah Onuora

ORIGINAL ARTICLE Gracey, E. et al. TYK2 inhibition reduces type 3 immunity and modifies disease progression in murine spondyloarthritis. *J. Clin. Invest.* https://doi.org/10.1172/JCI126567 (2020)
RELATED ARTICLE Ranganathan, V. et al. Pathogenesis of ankylosing spondylitis — recent advances and future directions. *Nat. Rev. Rheumatol.* **13**, 359–367 (2017)

GOUT

β-carotene blocks the inflammasome

The NLRP3 inflammasome has a prominent role in the pathogenesis of inflammatory arthritis, particularly gout. Several approaches are currently being explored to target the NLRP3 inflammasome as a strategy for the treatment of gout, most of which target the NACHT domain of NLRP3. A new study that aimed to investigate molecules that target the pyrin domain of NLRP3 suggests that β-carotene might have potential as a future therapy for gout.

"Although the antioxidant activity of β-carotene, a plant-derived provitamin A, has been widely reported, our study is the first report to provide the mechanistic detail as to how β-carotene supplementation might prevent NLRP3 inflammasome-related diseases such as gouty arthritis," states corresponding author Joo Y. Lee.

The researchers began by establishing β-carotene as a promising binding candidate for the pyrin domain of NLRP3. "We ran molecular docking modelling screening with ~62,800 compounds and selected β-carotene as an NLRP3 inflammasome inhibitor, then identified the direct binding mode between β-carotene and the pyrin domain of NLRP3 using surface plasmon resonance analysis and NLRP3 mutation experiments," says Lee.

In mouse models of gouty arthritis of the knee and foot, administration of oral β-carotene prior to injection with monosodium urate crystals reduced the severity of disease and prevented the production of IL-1β and caspase 1 (products of the NLRP3 inflammasome). Furthermore, the administration of β-carotene to cells from the synovial fluid of patients with gout reduced their secretion of IL-1β in a dose-dependent manner.

"Our findings suggest that pharmacological application of β-carotene might improve inflammatory symptoms related to the NLRP3 inflammasome, such as those experienced by patients with gout," concludes Lee.

Joanna Clarke

ORIGINAL ARTICLE Yang, G. et al. Direct binding to NLRP3 pyrin domain is a novel strategy to prevent NLRP3-driven inflammation and gouty arthritis. *Arthritis Rheumatol.* https://doi.org/10.1002/ART.41245 (2020)
RELATED ARTICLE So, A. K. & Martinon, F. Inflammation in gout: mechanisms and therapeutic targets. *Nat. Rev. Rheumatol.* **13**, 639–647 (2017)

RHEUMATOID ARTHRITIS

A drug delivery system with sting

Scientists have developed a new system for delivering drugs to cartilage in which the drug, in this case a glucocorticoid, is linked to a peptide found in the venom of scorpions. In a rat model of arthritis, this drug conjugate could reverse signs of arthritis without evidence of glucocorticoid-related systemic toxicity.

Cystine-dense peptides (CDPs) are a family a miniproteins found in a wide variety of species and are often used for predation or protection. In a biodistribution screen of 42 CDPs from 20 species, the researchers identified a group of CDPs that accumulate and persist for several days in the cartilage of rats and mice. They hypothesized that these molecules could be used to deliver drugs for the treatment of arthritis.

Further experiments found that they could conjugate one of the cartilage-accumulating CDPs, CDP-11R, to a fluorophore or dexamethasone, without substantially altering its localization to cartilage. The researchers made further amendments to the drug conjugate by introducing a labile linker that hydrolyses at a desirable rate in the plasma, on the expectation that steric hindrance could otherwise prevent the therapeutic effects of the conjugated drug.

"Unfortunately, the small amounts of dexamethasone that made it into the bloodstream were sufficient to cause adverse effects that we considered unacceptable for long-term treatment," explains James Olson, corresponding author of the new study. "We switched to triamcinolone acetonide (TAA) as the payload because TAA is rapidly metabolized to an inactive metabolite in the bloodstream." In rats with collagen-induced arthritis, various doses of the CDP-11R–TAA conjugate could reduce inflammation in the arthritic joints, without signs of systemic adverse effects (such as atrophy of the spleen or thymus).

"Our vision is to create a version of this drug candidate that patients would administer to themselves infrequently," explains Olson. "We hope that such a drug could provide arthritis relief with no or few adverse effects."

Jessica McHugh

ORIGINAL ARTICLE Cook Sangar, M. L. et al. A potent peptide-steroid conjugate accumulates in cartilage and reverses arthritis without evidence of systemic corticosteroid exposure. *Sci. Transl Med.* **12**, eaay1041 (2020)